REMARKS/ARGUMENTS

This is a response to the Office Action mailed January 15, 2004, in the above-identified application.

Associate Power of Attorney and
Change of Correspondence Address

Said Office Action was mailed to the firm of Senniger, Powers, Leavitt, and Roedel, who previously handled the prosecution of this application. It should be noted that the responsibility for prosecution of this application was recently transferred to the undersigned attorney. An ASSOCIATE POWER OF ATTORNEY and a CHANGE OF CORRESPONDENCE ADDRESS PTO FORM SB/122 were submitted to the PTO by Facsimile on October 21, 2003. A true photocopy of said submission is attached hereto for the record. Please note the change in Attorney Docket Number to 3030/US.

Present Office Action

Claims 37-75 were presented for examination in a previous response designated Amendment D. In the Office Action of January 15, 2004, the specification was objected to under 35 U.S.C. §112, first paragraph, and various of the claims were rejected under 35 U.S.C. §112, first and second paragraphs, and under 35 U.S.C. §103. In order to reduce the issues and facilitate the further prosecution of this application to allowance, the 39 pending claims have been reduced to a total of nine (9) claims, five of which are currently amended.

Thus, the remaining claims herewith presented for consideration are Claims 41-42, 51, 56-58, 61, 69 and 70. Claims 69 and 70 are independent, whereas the other seven (7) claims are dependent on Claim 70.

The Objection to the Specification

The specification was objected to under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to make and/or use the invention, and thereby failing to provide an enabling disclosure. This objection is traversed for reasons as follows:

The basis of the Examiner's objection appears to consist in a failure to set forth the criteria that defines those compounds envisioned as "nucleotide antiviral compound" or "nucleotide antiviral" useful for practicing the invention, and thereby necessitates undue experimentation.

As amended herewith, the aforesaid objected terms, "nucleoside antiviral compound" and "nucleotide antiviral" have been cancelled from the claims. These terms were previously used in generic Claim 70 to define a "second" compound illustrated by the approximately 36 specific compounds listed on pages 18-19 which are commonly known in the art as "nucleoside analogues". As amended herewith, the objected terms are replaced in the claims with the term:

"a second amount of an antiviral compound selected from the group consisting of

2',3'-dideoxycytidine (ddC).
2',3'-dideoxycytidine-5'-triphosphate,
(-)-2',3'-dideoxy-3'-thiacytidine,
(-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC)"

These four named compounds now recited in generic Claim 70 are closely related 2', 3'-dideoxy cytidine compounds or analogs thereof which are well-known in the art. The first two compounds in Claim 70 are commercially available, for example, from Sigma® Chemical Company, as seen from page 357 of its catalog of *Biochemicals and Reagents for Life Science Research* (copy attached). The third listed compound in Claim 70 and its synthesis are described in U.S. patent 5,539,116 (copy attached). The fourth listed compound in Claim 70 and its structure are shown in Figure 11 in the *Gish et al.* reference cited by the Examiner and

by the Applicant at page 4, lines 13-14. It should be noted that the *Gish et al.* reference classifies these compounds under the general heading: "Nucleoside analogues" at the top of page 102, right hand column.

The 2', 3'-dideoxycytidine compounds and their 5' triphosphate analogs have been known for many years as potent inhibitors of human acquired immune deficiency syndrome (AIDS) virus as can be seen from *Aldrichimica Acta*, Vol. 22, No. 2, 1989, page 47 (see copy attached).

Although the claimed invention is not concerned with how to make these commonly known antiviral compounds, the specification in the paragraph bridging pages 19 and 20, cites seven scientific publications for conventional methods of preparing these compounds. The specification also provides reasonable guidance for making these antiviral compounds at pages 16-20, including a list of 36 illustrative compounds which include the four (4) named in Claim 70.

In view of the above amendment to the claims, the well known synthesis and structure of the compounds recited in the claims, and the commercial availability of compounds in the group of 2', 3'-dideoxycytidines, it is respectfully submitted that the objection to the specification under 35 U.S.C. §112, first paragraph, should be withdrawn. It is a general rule of patent law that "a patent need not teach and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986). The specification also provides a reasonable amount of guidance with respect to the compounds recited in the claims. As stated by the Board of Patent Appeals and Interferences, "a considerable amount of experimentation is permissible if it is merely routine" or if the specification provides "a reasonable amount of guidance." *Ex parte Forman*, 230 U.S.P.Q. 546 (B.P.A.I. 1986).

Claims Rejection Under 35 U.S.C. §112

Claims 37-54, 58-66, 70-71 and 75 have been rejected under 35 U.S.C. §112, first paragraph, for the reasons specified in the objection to the specification. Of these claims,

claims 37-40, 43-51, 53, 54, 59-60, 62-66, 71 and 75 have been cancelled. The remaining retained claims have been amended as stated above and, therefore, overcome the Section 112 rejection for the same reasons that the objection to the specification has been overcome. Accordingly, it is respectfully submitted that the rejection under Section 112, first paragraph, should be withdrawn.

Claims 37-54, 58-66, 70-71 and 75 have been further rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is traversed for reasons as follows:

The basis of the Examiner's rejection appears to reside in the alleged indefiniteness of the phrases "nucleotide antiviral compound" or "nucleotide antiviral." As pointed out above, these phrases have been cancelled from the claims and replaced with the nomenclature of four well known, specifically named compounds. Accordingly, it is respectfully submitted that the rejection under Section 112, second paragraph should be withdrawn.

Claims Rejection Under 35 U.S.C. §103

Claims 37-75 have been rejected under 35 U.S.C. §103 as being unpatentable over *Partis, et al., Chang et al., and Gish, et a*l. This rejection is traversed for reasons as follows:

As stated above, the 39 pending claims have been reduced to a total of nine (9) claims, five of which also are currently amended. The retained nine (9) claims are Claims 41-42, 52, 56-58, 61, 69 and 70. Claims 69 and 70 are independent, whereas the other seven (7) claims are dependent on Claim 70. Claim 70 is a generic claim, and Claim 69 recites a preferred embodiment within the scope of Claim 70.

Applicant notes and appreciates the Examiner's statement at the end of page 10 of the Office Action, that: "Examiner would favorably consider claims directed to those medicaments

providing unexpected therapeutic benefits, as averred herein." It is respectfully submitted that in good faith reliance upon the Examiner's suggestion, the claims are amended herein to recite medicaments providing the unexpected therapeutic benefits as averred herein.

Applicant's claimed invention as amended relates to a pharmaceutical composition comprising the combination of two different groups of antiviral compounds which are disclosed as "preferred" compounds or very close analogs thereof. Preferred compounds in the first group are identified at page 14, lines 20-22, and in the second group at page 19, lines 32-33. That is, preferred compounds of the first group are stated to be N-(n-nonyl-)-1,5-dideoxy-1,5-imino-D-glucitol and N-(nonyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate; and of the second group a preferred compound is (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC).

The claims as amended now recite these preferred compounds and very close analogs thereof that are reasonably believed to have the unexpected properties of anti-hepatitis B virus activity illustrated in Examples 3-5 at pages 33-42. Thus, in Example 3, it is concluded that the results demonstrate that: "the combined effect of 3TC plus N-nonyl-DNJ is greater than that of either compound alone, or the additive individual effects of each compound." It is respectfully submitted that these results thus demonstrate unexpected therapeutic benefits.

In the generic Claim 70 as amended herein, the first amount of the N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds of Formula I is limited to compounds in which the R is a straight chain alkyl having a chain length of 7-12 carbon atoms, which reasonably encompasses the illustrative n-nonyl, and in which W, X, Y, and Z are limited to hydrogen or butanoyl, and the second amount of an antiviral compound is limited to the four named 2',3'-dideoxycytodine or 2'-deoxy-3'-thiacytidine compounds and their 5'-triphosphate analogs. It is respectfully submitted that the prior art does not teach the unexpected anti-hepatitis B virus benefits obtained with this claimed combination of compounds.

The Partis et al., Chang et al., and Gish et al., references

It is noted that there are several *Partis et al.* patents cited in the record of this

application. It is assumed that the Examiner has applied the *Partis et al.* reference cited as U.S. Patent No. 5,221,740 in the Notice of References Cited, PTO-892, with the Office Action mailed March 21, 2003. This conclusion is based on the Examiner's comment in said Office Action concerning Examples 13 and 16 of *Partis et al.*

Applicant acknowledges that in Examples 13 and 16, *Partis et al.* teach the synthesis of N-(nonylimino)-1,5-dideoxy-D-glucitol and 1,5-(butylimino)-1,5-dideoxy-D-glucitol, tetrabutyrate, and that these and similar compounds are disclosed as antiviral compounds which can be used in formulations with pharmaceutically acceptable diluents and carriers. However, the only disclosed antiviral activity is activity against human acquired immunodeficiency syndrome (AIDS) virus and anti-lentivirus activity. See, for example, Example 43 of *Partis et al.,* in which the only activity shown is against AIDS virus or lentivirus. There is absolutely nothing whatsoever in *Partis et al.* which relates to anti-hepatitis virus activity.

Although *Partis et al.* mentions the compound 3'-azido-3'-deoxythymidine (AZT), at col. 1, line 58, to col. 2, line 2, that compound is merely acknowledged as a known anti-AIDS compound. *Partis et al.* does not teach or suggest using AZT or any other nucleoside analog in combination with the disclosed N-nonyl-DNJ analogs. In any event, the AZT is not included in applicant's amended claims, all of which relate to pharmaceutical compositions useful for treating hepatitis virus infections as distinguished from other virus infections.

Chang et al., U.S. Patent No. 5,750,648, teaches the use of retroviral protease inhibitors in combination with other anti-HIV compounds, e.g., N-butyl-DNJ or nucleotides. However, the only activity data disclosed in *Chang et al.* relates to treatment of acquired human immunodeficiency syndrome (AIDS) virus or HIV, as seen from Example 29 of *Chang, et al.*

All of the viruses mentioned by *Chang et al.* are related to HIV, e.g., HIV-1, HIV-2, HTLV-1, HTLV-2, VIS-A, and SIV, as described at col. 31, lines 17-27. There is no mention whatsoever of any hepatitis virus.

Most significantly, the retroviral protease inhibitors disclosed by *Chang et al.* to produce the desired inhibitory activity are defined as "urea-containing hydroxyethylamine inhibitor compounds". See col. 2, lines 30-32. The biological activity disclosed and taught by *Chang et al.* with these retroviral protease inhibitors is activity against human acquired immunodeficiency syndrome virus. There is no teaching concerning anti-hepatitis activity.

Although *Chang et al.* mentions that the retroviral protease inhibitors "can be used in combination with two or three other antiviral agents which are effective against HIV-1", such as various "nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, tat antagonists and glycosidase inhibitors", at col. 33, lines 22-33, and Claim 16, the combination requires the presence of the urea-containing hydroxyethylamine inhibitor compounds to obtain the desired anti-HIV activity. There is no suggestion that these other compounds can be used in combination by themselves in the absence of the urea-containing hydroxyethylamine compounds. Nor is there any activity data shown with any of these other compounds either by themselves or in combination, for activity against hepatitis virus or any other virus. Moreover, there is no suggestion in *Chang, et al.* to use N-nonyl-DNJ in these combinations. Only the N-butyl-DNJs are disclosed. See col. 34, lines 16-18, and Claim 17.

Gish, et al., Exp. Opin. Invest. Drugs **1995**, 4(2), 95-115, discloses a variety of substances for treatment of hepatitis B virus, e.g., nucleoside analogues as mentioned above, and various other substances. "Combination treatment" is described in a section so labeled at pages 107-110. Although various other agents for the combination treatment are listed, e.g., in Table 6, at page 109, there is absolutely no mention of N-nonyl-DNJ or other N-alkyl-DNJ type compounds.

None of the cited references, either alone or in combination, teach the advantageous anti-hepatitis activity obtained with N-nonyl-DNJ or its close analogs in combination with 3TC or its close analogs as claimed in applicant's amended claims. As stated in Example 3: "the combined effect of 3TC plus N-nonyl-DNJ is greater than that of either compound alone, or the additive individual effects of each compound." It is respectfully submitted that these results thus demonstrate unexpected therapeutic benefits unobvious from the cited prior art.

In view of the above remarks, it is submitted that all of the Claims retained herein and as amended, namely, Claims 41-42, 52, 56-58, 61, 69 and 70, are patentable over the art in accordance with 35 U.S.C. §103, and together with the specification satisfy the requirements of 35 U.S.C. §112, paragraphs one and two. Accordingly, allowance thereof and an early Notice of Allowance is courteously solicited.

Respectfully submitted,

Scott J. Meyer, Reg. No. 25,275
Attorney for Applicant

April 8, 2004

SJM/mrr

April 2, 2004